Reproductive Endocrinology: Puberty, Menopause, and the HPO

Introduction

Reproductive endocrinology is a subspeciality of OB/GYN. Therefore, this lesson is very clinically oriented—taking a complaint and making a diagnosis. In fact, each section (except for the first) gets its own dedicated lesson in Clinical Sciences. Here, as we did so often in Endocrine, we start with the diagnosis and explain the pathogenesis. This is how the Basic Sciences exposes you to clinical content while keeping you oriented toward mechanisms rather than management. You have seen the elements of this system before in Male Reproduction #2: *Sexual Differentiation Inside and Out* (but now we add the complexity of puberty to genetics and hormones), Female Reproduction #1: *The Healthy Ovary* (from the perspective of the ovarian cycle), and Female Reproduction #2: *The Healthy Uterus* (from the perspective of the uterine cycle). You will see the hypothalamic-pituitary-ovarian (HPO) axis again in the context of pregnancy and pregnancy-related changes in the Pregnancy and Delivery island. The repetition with a different focus is intentional. As far as endocrinology goes, female reproductive endocrinology has the least well-elucidated mechanisms and the most complex feedback mechanisms.

We're going to explore puberty, problems with puberty (precocious puberty and delayed puberty), amenorrhea (primary and secondary), and polycystic ovary syndrome (PCOS), then close with menopause.

We assume that you have already mastered the content in Female Reproduction #1: *The Healthy Ovary* and are comfortable with □ and the ovarian cycle.

Puberty

The awakening of the HPO axis kicks puberty into gear. That awakening is a yet unelucidated process that is believed to be driven by the limbic system and other deep brain structures. Likely, the source of that signal is □, the center that facilitates the LH surge. Because too little is known about it, you don't have to know about it.

But what *is* known is that **once awoken, the axis doesn't shut off**. That means that in the case of precocious puberty—early onset of pubertal changes (as below)—due to a tumor that secretes ovarian hormones, if the tumor is removed, puberty will still continue, and the girl will have her axis suppressed by continuous GnRH analogs (more on this in Breast #2: *Breast Pathologies Not Cancer*). □ is supposed to awaken the axis, but the axis can be awoken through other pathologic mechanisms.

Female sex hormones that drive the proliferation and maturation of the female body are primarily estrogens, which we refer to only as **estrogen**. Progestins tend to regulate estrogens through negative feedback, and similarly, we refer to the collective progestins as **progesterone**. That means we use only estrogen and progesterone but know that they represent a category of hormones. Unlike the simplification of estrogen and progesterone, we will continue to use the nebulous term **androgens** to imply testosterone from the gonads and DHEA from the adrenal glands, and where necessary, specify the class of androgen: adrenal androgens (DHEA) or gonadal androgens (testosterone).

The awakening of the HPO axis does more than make estrogen. It also initiates changes in the **growth hormone** axis, leading to the pulsatile release of growth hormone-releasing hormone (GHRH) and the episodic production of growth hormone (GH), which in turn creates a steady increase in insulinlike growth factor 1 (IGF-1; Endocrine: Pituitary #3: *The Unhealthy Posterior Pituitary*), inducing the onset of growth. Soon after puberty begins, the hypothalamic-pituitary-adrenal axis also awakens, and the **adrenal glands** begin producing the adrenal androgen **DHEA**.

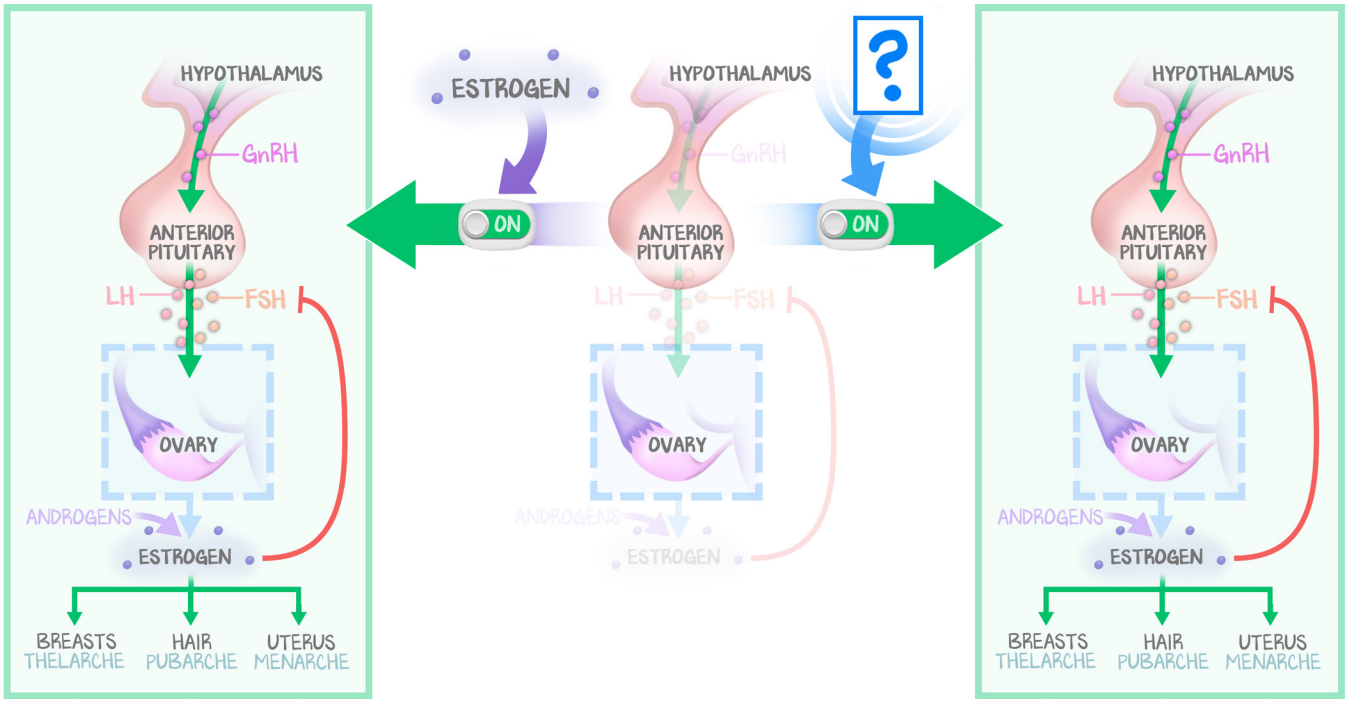

Figure 6.1: Once Awoken, Never to Sleep (Until Menopause)
The mysterious, elusive ? in the hippocampus is supposed to initiate puberty, turning on the HPO axis at the right time. Once it does, estrogen is made, and ovarian cycles cycle until pharmacology, pregnancy, or menopause turns them off. If something outside the axis generates estrogen, the axis will awaken, and the ovarian cycles will cycle. Even if the primary pathology (e.g., an estrogen-secreting tumor) is removed, the axis has already been awoken, and so without pharmacological intervention, precocious puberty is inevitable.

The changes in the pubertal female are a **growth spurt** (the long bones get longer because of the growth hormone axis, culminating in the fusion of the epiphyseal plates), the acquisition of **secondary sex characteristics** (breast development, pubic hair, and axillary hair because of estrogens), and the initiation of the uterine cycle driven by the ovarian cycle hormones, evidenced by **menses**.

The timing of puberty varies widely. What comes next is meant as a ballpark estimate, keeping in mind that "normal" encompasses both the 8-year-old whose careful pediatrician notices early signs of breast bud development and the 14-year-old who hasn't started puberty yet (whose mother's puberty began at 15). The mean age at the onset of puberty for girls is 10. In general, thelarche (breast budding) is the first clinical sign of puberty in girls, followed by pubarche (pubic hair development), although these are reversed in approximately 15% of cases. Tanner staging is used to describe the stages of breast and pubic hair development during puberty. Other -arche words you may encounter are adrenarche (initiation of adrenal hormones), menarche (onset of menses), and gonadarche (growth of ovaries and testis, noticed in males via increases in scrotum size).

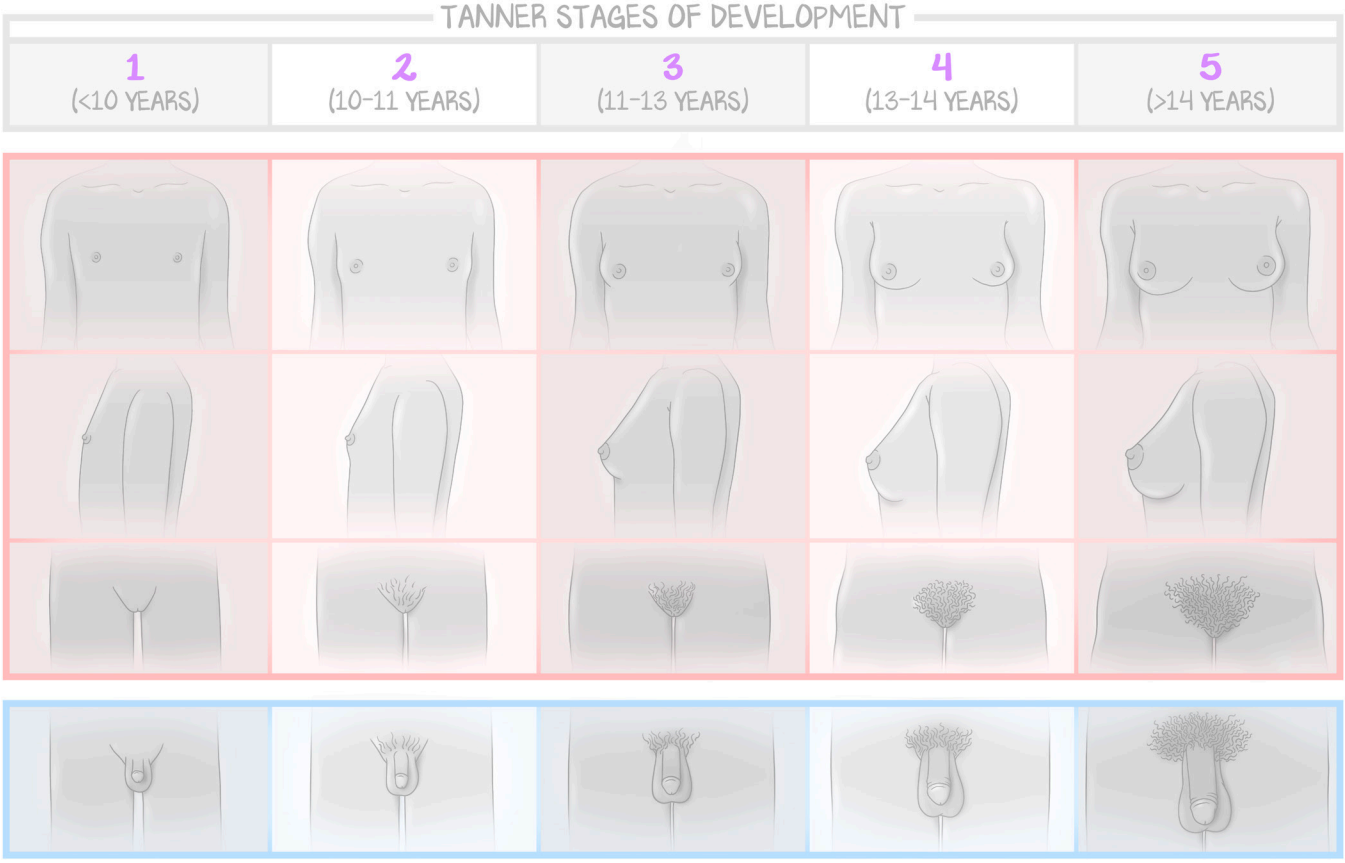

Figure 6.2: Tanner Stages of Development
In both sexes, axillary and pubic hair develop. The more hair, the further along in puberty the child is. For males, the testes increase in size, and thus the size of the scrotum (often in parallel with the size of the penis) denotes the maturation of the gonads. In females (whose ovaries in the pelvis are not visible as are the testes are in the scrotum), there is no means of monitoring gonad size. In females (who have breast development where no such development occurs in males), the Tanner stages are dependent on the progression from breast buds to the adult contour. You will not be asked to identify which Tanner stage a person is in on a licensing exam, but you may be given a Tanner stage development to denote progression through puberty. Tanner stage 1 is the earliest stage. Tanner stage 5 is the adult form.

Menarche follows approximately 2 to 2.5 years after thelarche. The pubertal growth spurt often begins before thelarche, but the peak height velocity usually occurs just prior to menarche and coincides with Tanner stage 3 breast development. The onset of puberty varies. Family history is a strong predictor of the timing of pubertal development. The age of the patient's mother at the time of menarche is a strong predictor for her age at menarche. Racial differences in pubertal development have been identified, with African-American girls entering puberty at earlier average ages than their non-Hispanic white counterparts. Higher BMI has also been linked to earlier onset of puberty.

Precocious Puberty

Precocious puberty is defined by the onset of pubertal changes while too young to be having them. The age varies and may need to be adjusted for race and family history, but what we want you to learn is **8 years old**. If younger than 8 years old and there is any sign of pubertal onset, deem it precocious puberty (it's 9 years old for boys: girls really do "develop faster" than boys).

Precocious puberty has been broken down in an interesting way. Although most endocrinopathies are named primary (the effector organ is the problem) and secondary (something above the effector organ is the problem), the endocrinopathy of excess ovarian hormone causing precocious puberty isn't classified that way. Instead, there is central vs. peripheral. **Central precocious puberty** (CPP) is driven by excess GnRH (hypothalamic) or excess FSH/LH (anterior pituitary), whereas **peripheral precocious puberty** (PPP) is driven by excess estrogen (ovary) or androgen (DHEA). Precocious puberty is caused by excess or **early estrogen receptor activation**. Excess estrogen induces the activation of estrogen receptors (that one is obvious). Excess androgens can also activate the system in two ways: in the peripheral tissues (adipose), small elevations in androgens are converted to estrogen, and large elevations in androgens can activate estrogen receptors even without conversion to estrogen (though with weak affinity).

Excess androgens will also result in virilization—the masculinizing of the female phenotype. So, although both androgen problems (such as congenital adrenal hyperplasia) and estrogen problems (such as an ovarian tumor) initiate puberty, additional symptoms will be present if the underlying pathology is excess androgen. Virilization and hirsutism are covered in detail in the Clinical Sciences.

Evaluation involves the assessment of hormone levels. Because there is increased activation signaling, the cyclic changes seen with follicular cycles and ovulation won't be present, enabling (for the most part) the representation of these conditions in classic endocrine feedback. **Estrogen is elevated**, estrogen starts puberty, and estrogen will subsequently inhibit the HPO axis. In all cases, estrogen not only starts puberty early but also increases proliferation, increasing this girl's risk for future endometrial, ovarian, and breast cancer. The sooner it is corrected, the less affected she will be.

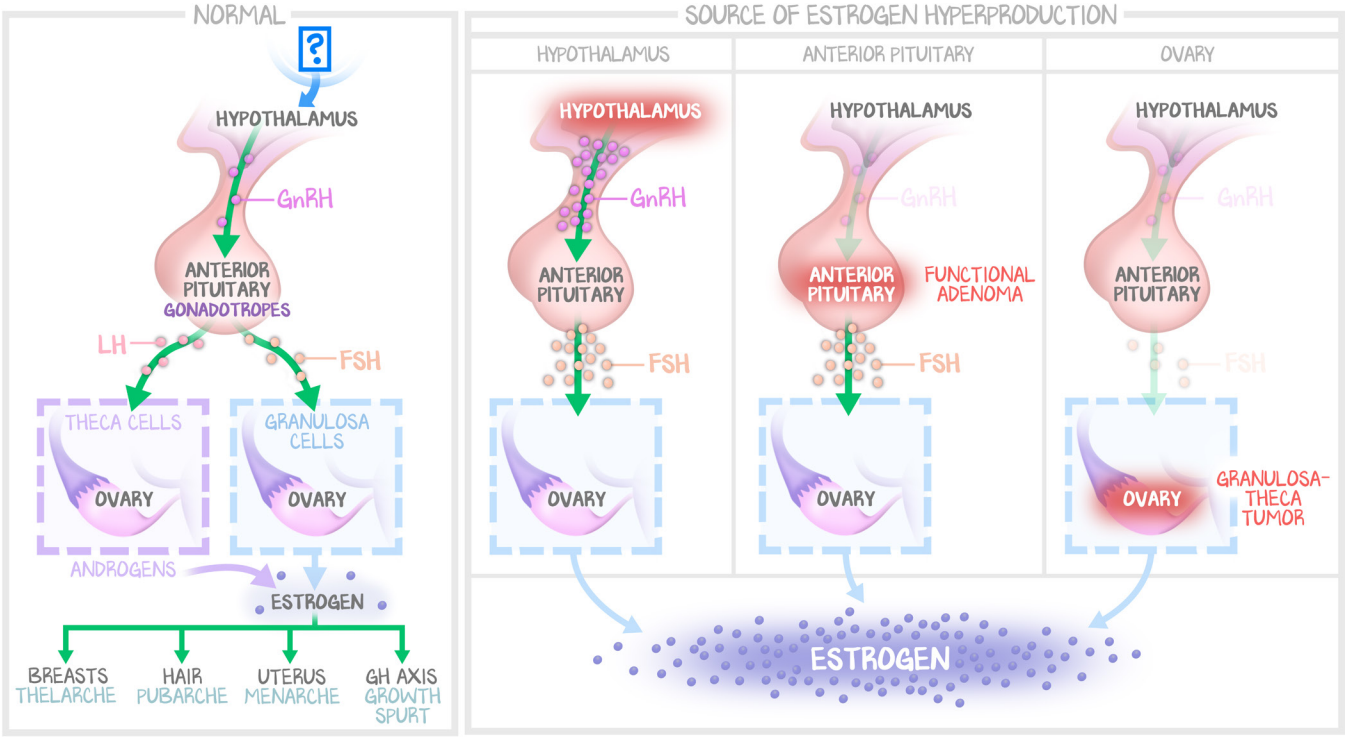

Figure 6.3: Precocious Puberty Axis
No matter the original etiology, with excess estrogen, puberty is kicked into gear. You can think of this axis as having traditional feedback inhibition, so the hypothalamus and anterior pituitary are inhibited when excess estrogen is produced. If the source of hyperproduction is the hypothalamus, FSH and estrogen levels will be elevated. If the source of hyperproduction is the anterior pituitary, FSH and estrogen will also be elevated (because GnRH is pulsatile, it is not obtained clinically but would be "decreased" if staying rigid to the method). If the source of hyperproduction of estrogen is the ovary, the hypothalamus and anterior pituitary would be silenced, resulting in low FSH and high estrogen.

Whenever a patient presents with early-onset puberty, the first step is to assess **bone age** with an X-ray. Bone age is determined by the growth plates. With precocious puberty, the worry is that the girl's menarche will come too soon. When [redacted] awakens the axis, it awakens all the axes—GnRH, GHRH, CRH. When something else awakens the HPO axis (estrogen), the other axes will also awaken but out of sync with the normal timing. The growth spurt is supposed to coincide with the onset of menses. But if the HPO axis matures before the growth hormone axis, her growth plates may fuse ahead of her growth spurt. Once confirmed to be in precocious puberty, the next step is an **LH level**, which narrows the possible diagnosis to gonadotropin-independent (LH is low, look in the abdomen and pelvis with **ultrasound** or **MRI**) or gonadotropin-dependent (LH is high, look in the brain with **MRI**). If uncertain, a GnRH stimulation test may facilitate the diagnosis.

Central causes of precocious puberty will demonstrate elevated gonadotropins. Peripheral causes of precocious puberty will demonstrate decreased gonadotropins.

If a **mass** is producing a hormone, that mass is resected. Because puberty has been initiated, she will require medical treatment even after the removal of the mass. Medical treatment artificially silences the axis until her actual age matches or is near to her bone age. Suppression of the axis is achieved with **continuous** (as opposed to pulsatile) **GnRH analogs** such as **leuprolide**. When the treatment is discontinued, her ovaries are allowed to progress in their normal (age-adjusted average) time. GnRH pulsatility drives follicular cycles and ovulation. Continuous GnRH silences the axis.

Delayed Puberty

In MSK, we talked about how the most common cause of delayed puberty is **constitutional growth delay**—if you wait and do nothing, the child will enter puberty and grow normally. As with precocious puberty, the right move is usually just to wait. Here we discuss only the causes of delayed puberty related to **hypogonadism**. Hypogonadism is the generic term for too little sex hormone (no estrogen in girls, no testosterone in boys). Again, unlike most endocrinopathies, which are classified as primary (the gonad) or secondary (the axis), delayed puberty uses a different classification. This is because the delayed puberty is merely a symptom of the underlying condition. There is too little sex hormone, so both categories are hypogonadism. If the problem is the axis, then the cause is deficient production of the **gonadotropins** (LH and FSH); this is termed **hypogonadotropic hypogonadism**. If the problem is the gonads, then the axis will be disinhibited, and the anterior pituitary will produce excess gonadotropins (LH and FSH); this is termed **hypergonadotropic hypogonadism**.

If there is a problem with generating the signal, but the ovary is healthy and can hear the signal fine, then **the axis is bad** (hypogonadotropic hypogonadism). The cause is either failure of the hypothalamus to release GnRH or failure of the anterior pituitary to release LH and FSH. Evaluation begins with an FSH and LH level (which will be low) and a **GnRH stimulation test**. FSH and LH levels are measured before and after the administration of a pulse of GnRH. We are starting with a hypogonadotropic state and assessing whether or not the cause is the pituitary. If the pituitary is normal, then the GnRH stimulus will increase FSH and LH, identifying the hypothalamus as the problem. If the LH and FSH values don't elevate, the problem is the pituitary itself. In both cases, having already identified the cause to be within the axis, an **MRI** is obtained to evaluate both the hypothalamus and pituitary.

Despite the rarity of these conditions, they make excellent fodder for licensure examinations. The causes we want you to learn are Kallmann syndrome, panhypopituitarism, and pituitary tumor. The syndrome associated with hypothalamic failure is **Kallmann syndrome**, presenting with the combined symptoms of **anosmia** and **absent GnRH-secreting neurons**. Both the olfactory sensory neurons and GnRH-secreting neurons of the hypothalamus must migrate into their positions. A failure of both results in the inability to smell and delayed puberty. A number of causes are traced back to the anterior pituitary,

such as **panhypopituitarism** (which is rare in a child but can be part of the autoimmune-endocrine overlap that includes diabetes type 1, adrenalitis, and thyroiditis, or a past pituitary resection) or an **anterior pituitary adenoma/craniopharyngioma**. As we discussed in panhypopituitarism in Endocrine (Endocrine: Pituitary #2: *The Unhealthy Anterior Pituitary*), the more-crucial-for-life functions are spared while the gonadotropes are the first to lose function, so there may be no symptoms of the growing mass.

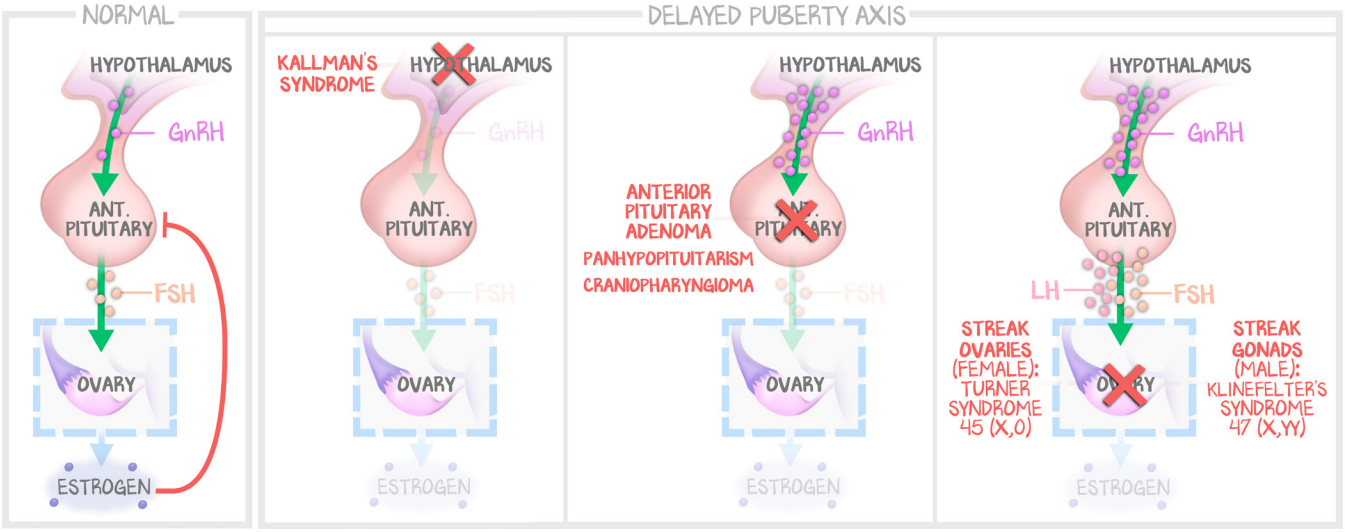

Figure 6.4: Delayed Puberty Axis
In each condition, the result is low estrogen. However, the FSH level varies depending on the condition. When the cause is in the brain—a defect in either the hypothalamus or the anterior pituitary—deficient FSH results in deficient estrogen. When the problem is the ovaries, the anterior pituitary increases its signal, increasing FSH in response to deficient estrogen.

If there is a problem with the ovary, and the axis is healthy, the ovary will be unable to perceive the signal—the gonads are bad. If the axis is healthy, then the hypothalamus and anterior pituitary will respond to the absence of sex hormone negative feedback inhibition. In other words, they will yell louder to try to get the ovaries to do what they are supposed to do. They "respond to the absence of feedback inhibition" and "yell louder" by increasing GnRH pulsatility, thereby **increasing FSH and LH**. But because the gonads are bad, despite **elevated FSH and LH,** there will be a **low estrogen** level (or testosterone level in boys). The syndromes that cause this form of delayed puberty are usually diagnosed prior to puberty, and delayed puberty is generally more of an anticipated problem than the symptom leading to the syndrome's diagnosis. The classic example in girls is **Turner syndrome (45,XO)**, where the ovaries are nothing but fibrotic streaks. The classic example in boys is **Klinefelter syndrome (47,XXY)**. These diseases' illness scripts are discussed in detail in Biochemistry: Genetics #6: *Chromosome Number Diseases*. Patients with dysfunctional gonads require supplementation of their sex hormones to progress through puberty normally.

Primary Amenorrhea

Related to delayed puberty but with slightly different considerations is the condition of **primary amenorrhea**—a girl who has never had a menstrual cycle. The age at which investigation should begin is constantly being adjusted; **13**, **15**, and **3 years later** is what we want you to commit to memory. Suspect delayed puberty if there has been no onset of any secondary sex characteristics (no pubic hair or breast development) by 13, no menarche by age 15, or the girl is younger than 15 but more than 3 years past the onset of thelarche. Using the physical exam, a point-of-care pelvic ultrasound, and some bloodwork (FSH, LH, TSH, and urine pregnancy test), you can arrive at an answer fairly quickly.

You're testing for **anatomy** and **the axis**. In order to have menses, the girl must have a uterus and sex hormones to inform the uterus to proliferate, secrete, and slough.

The axis is assessed with the physical exam, identifying the presence or absence of **secondary sex characteristics**. Because secondary sex characteristics require estrogen production, the presence of secondary sex characteristics tells you that the **axis is working**. The absence of secondary sex characteristics means the **axis is not working**. Suspicions are confirmed by estrogen, FSH, and LH levels, but the physical informs you of what to anticipate in those labs. If the axis is working, the FSH level will be elevated.

Anatomy is assessed using a **pelvic ultrasound**. The assessment is of the Müllerian ducts, tubes, and specifically, a uterus. If she has a uterus on ultrasound, she is said to be anatomy positive. If she has no uterus, then she is anatomy negative.

This method categorizes the various conditions into four quadrants—axis working or not working on the x-axis, with anatomy present or absent on the y-axis.

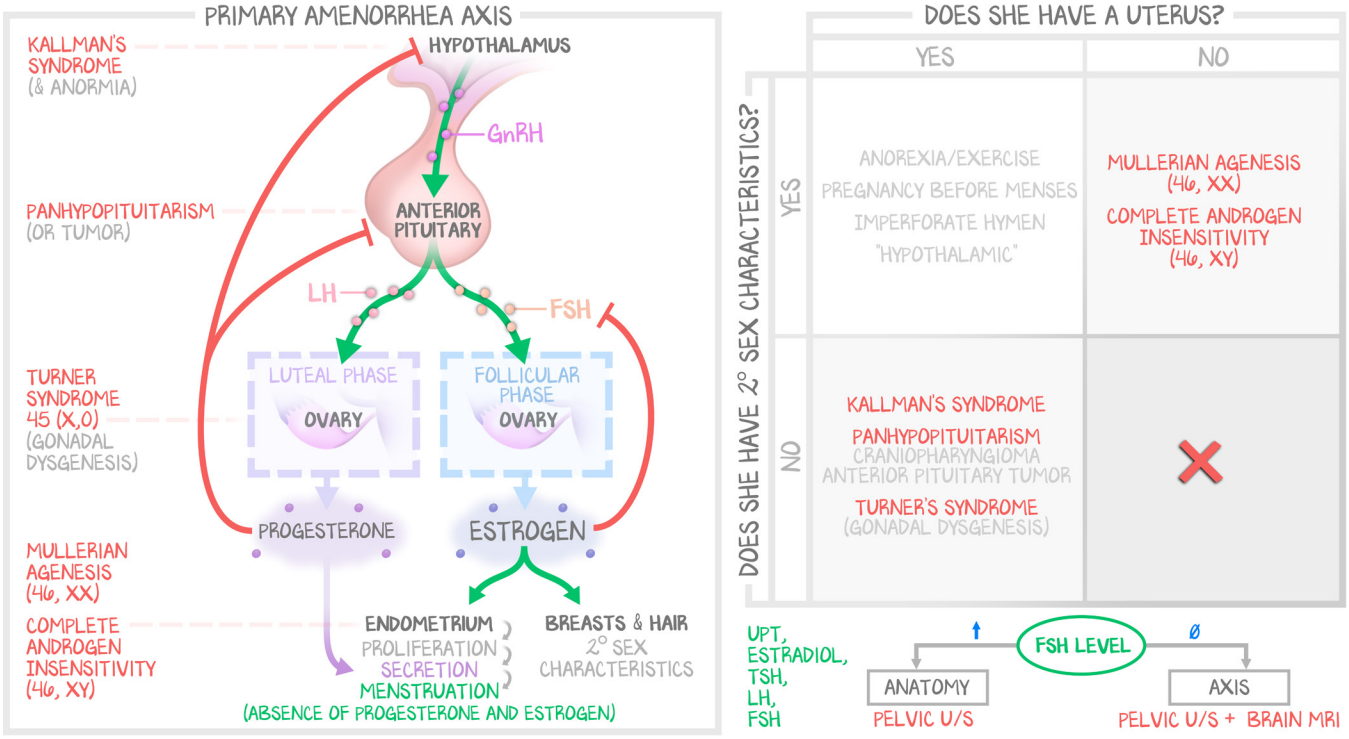

Figure 6.5: Primary Amenorrhea Axis
Primary amenorrhea is a slightly different problem from delayed puberty, with the added complexity of separating the uterine endometrium and secondary sex characteristics. The failure of menarche could be due to the hypothalamus, anterior pituitary, ovaries, or endometrium. Because of the split secondary sex characteristics and endometrial function (axis and anatomy), the causes of primary amenorrhea can be thought of as being in one of four quadrants, with the negative-negative causes not worth mentioning. In clinical practice, the work-up is much simpler, obtaining all the necessary tests up front, separating it into FSH-deficient hypogonadotropic hypogonadism and increased-FSH hypergonadotropic hypogonadism. We explore this more in the Clinical Sciences.

We have already played the coming game in sexual differentiation of a neonate, but it gets slightly more complex here because now we've introduced puberty, where the default phenotype is to do nothing. Neither male nor female puberty is the default; female puberty requires estrogen.

	GONADS	FEMALE TUBES	MALE TUBES	GENITALIA	BREASTS
IS THERE . . .	SRY/TDF?	AMH?	TESTOSTERONE?	DHT?	ESTROGEN?
Normal (46,XX)	No = Ovaries	No = Female	No = Involute	No = Female	Yes = Breasts
Normal (46,XY)	Yes = Testes	Yes = Involute	Yes = Male	Yes = Male	No = No development
Pure gonadal dysgenesis (46,XY)	Yes = But streak	No = Female	No = Involute	No = Female	No = No development
Complete androgen insensitivity (46,XY)	Yes = Testes	Yes = Involute	No = Involute (No internal phenotype)	No = Female	Yes = Breasts
Müllerian agenesis (46,XX)	No = Ovaries	No = But involute anyway	No = Involute	No = Female	Yes = Breasts
Turner syndrome (45,XO)	No = But streak	No = Female	No = Involute	No = Female	No = No development

Table 6.1: Expanding on Hormone Development into Puberty

Secondary Amenorrhea Causes (Down the Axis)

Secondary amenorrhea is the absence of menses in girls or women who had prior menses. In patients with previously regular cycles, amenorrhea requires evaluation after the absence of menses for 3 months or after an absence of 6 months if she has a history of irregular cycles. This next discussion is an academic one, not the order in which you order tests, but the order in which you should think of evaluating the axis. Specifically, secondary amenorrhea should be evaluated sooner if an underlying cause is suspected (e.g., pregnancy or other signs and symptoms of the etiology in addition to amenorrhea).

The cessation of menses means that there could be a problem with the uterus, ovaries, or axis (hypothalamus and pituitary). And that is the organizer—similar to the ovarian axis, only now we include the uterus. We work our way down the axis, exploring the different causes of secondary amenorrhea.

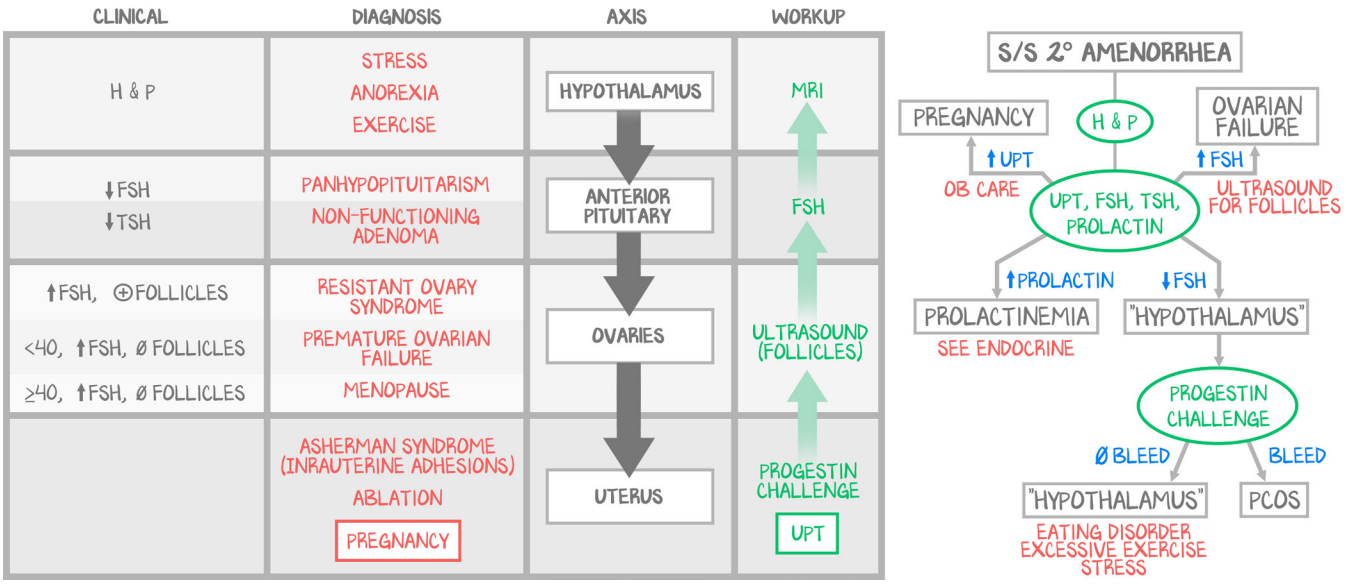

Figure 6.6: Secondary Amenorrhea Axis and Work-up
Secondary amenorrhea is only considered in a woman who previously had menses and has stopped having menses. This means that all of the rare causes of primary amenorrhea need not be considered. Again, the axis is the organizer, with the causes listed next to their corresponding roles in the axis. The organizer works down the axis, hypothalamus to uterus. The diagnostic workflow, listed to the right, relies heavily on the history, physical, and routine labs—urine pregnancy test, FSH, prolactin, and TSH with free T_4. Using these routine labs, a diagnosis of pregnancy, prolactinemia (covered in Endocrine), or ovarian failure (menopause if over age 40; premature ovarian insufficiency [POI] if under 40) can often be made. However, there are other considerations. Typically, the reason a woman has menorrhea is either obvious from the history and physical (e.g., eating disorder, excessive exercise, physical or emotional stress) and no work-up is required, or it's due to anovulation secondary to PCOS, which is diagnosed separately and not usually included in the work-up for secondary amenorrhea. The method used to evaluate each organ of the axis is listed to the right of the corresponding organ. A urine pregnancy test is always done first. A progestin challenge is used in patients with low FSH when no other diagnosis has been found. This used to be how PCOS was diagnosed, but now that the illness script is more robust, it is rarely performed. Ultrasound of the ovaries assesses for follicles—there are none in menopause and POI, but some may be present in resistant ovary syndrome (formerly called Savage syndrome). FSH and TSH levels assess the anterior pituitary and thyroid axis, and MRI can evaluate the brain. MRI is often not needed, but it's a diagnostic "last resort" after all other diagnoses have been excluded or when a pituitary mass is expected.

Hypothalamic causes are, in fact, quite common, accounting for 20% of secondary amenorrhea. They are a diagnosis of exclusion—what you find when you can't find anything, typically categorized as functional amenorrhea (caloric restriction, excessive exercise) and "other." Because reproduction is of the lowest concern to the host organism (mom has to be alive to reproduce), the body often sacrifices reproductive endocrine function first. Look for a competitive athlete who is otherwise very healthy or a girl who appears malnourished—weight loss, low body mass index, and any evidence of body dysmorphic disorder (covered in Psychiatry).

The **anterior pituitary** can fail to release LH and FSH if there is a **pituitary mass** consuming the anterior pituitary or worsening **panhypopituitarism**. As we said above, panhypopituitarism is uncommon in children, so it is unlikely to cause primary amenorrhea. Adults, especially women, are at increased risk for autoimmune destruction of the pituitary, as well as states where there can be acute loss of function, such as **Sheehan's** (panhypopituitarism in an adult female who lost a lot of blood and went hypotensive during delivery) or **apoplexy** (infarction of a pituitary adenoma). If the anterior pituitary is the cause, **FSH and LH levels will be low**, and any stimulation test will fail to stimulate. Look in the brain using **MRI**. The most common form of pituitary adenoma (discussed alongside other causes of prolactinemia in Endocrine: Pituitary #2: *The Unhealthy Anterior Pituitary*) is **prolactinoma**. In women, this usually presents as galactorrhea and amenorrhea due to high prolactin. The topic of prolactin returns in the Breast island, where we cover the physiological regulation of breast milk production in Breast #1: *The Healthy Breast*.

Because she had menses at one point, the ovarian causes can be only **menopause** or **premature ovarian insufficiency (**POI, also called premature ovarian failure, POF). POI is menopause that comes too early. The entire evaluation will be the same as that for menopause—**high FSH/high LH** and **no follicles** in the ovaries. Labs and imaging aren't needed to confirm normal menopause but should be evaluated to identify POI. Both patients will go through menopause, are at risk of menopausal symptoms (see below), and require menopausal management. The only difference between POI and normal menopause is age. Although menopause typically happens around age 50, the earliest menopause can be diagnosed is age 40. If menopause happens before 40, it is called POI and often associated with some genetic syndrome.

The **uterine causes** of secondary amenorrhea are anatomical or due to **adhesions/scarring**. Anatomical causes are more commonly associated with primary amenorrhea (imperforate hymen, bicornate uterus, septate vagina, etc.). Adhesions/scarring go by the eponym Asherman syndrome. **Asherman syndrome** is amenorrhea resulting from intrauterine adhesions that are **unintentionally iatrogenic**, forming after vigorous endometrial curettage or other uterine surgeries. When the scarring of the endometrium is **intentionally iatrogenic** (as in endometrial ablation for heavy bleeding in a woman who no longer desires fertility), it's not called Asherman syndrome. The point is, if there is a uterine cause of secondary amenorrhea, it's usually one that results in both amenorrhea and infertility.

Clinical Secondary Amenorrhea

Now, after that discussion of using the axis as the organizer and leaving the "work-up in reverse" only for the illustration, we want to make something really clear.

You are not going to give a progestin challenge to someone who hasn't had a history and physical or gotten a urine pregnancy test, but who has a bunch of labs done. Because efficient healthcare delivery balances cost (unnecessary testing) with efficiency (going to the lab 15 separate times versus the panel up front), you're going to take care of the usual suspects. After a history, physical, and point-of-care ultrasound performed by you in the office, it is reasonable to order a UPT, TSH, FSH, and prolactin all at once. You immediately rule out the common causes—pregnancy, hypothyroidism, prolactinemia, medications that could cause prolactinemia—and clinical reasoning leads you to a probable diagnosis. If the lab work shows **elevated FSH**, then it's looking like menopause or POI. Either way, she is treated like she has menopause. If the **FSH levels are low**, it is one of the other ones. This is where your suspicions from the history and physical can be tested. If she has signs of increased intracranial pressure (headache, vomiting without emesis, blurry vision), get the MRI, as there may be a mass. If she's an 18-year-old competitive gymnast trying out for the Olympics and works out in her sleep, that's probably the cause ("functional amenorrhea"). If her history includes an endometrial ablation for heavy menses, you probably shouldn't have bothered with the lab work. The point of this section isn't for you to learn when to do a progestin challenge, it's to implement the knowledge you've learned so far in a new, clinical way.

Polycystic Ovary Syndrome (PCOS)

The single most common endocrine disorder of women in the reproductive ages (6%–10%), which affects all races and genetic makeup equally, is PCOS. There are many variants on this condition, and they are based on permutations of the diagnostic criteria. There isn't much known about the underlying mechanism, but as we've done in our course, we're going to implement what we've already taught you to see whether we can deduce what others have not (probably not) and also reinforce the things you've learned in a different way. The diagnosis of PCOS is made by identifying **polycystic ovaries** (many mature follicles that do not ovulate and, therefore, accumulate), abnormal menses as indicated by **anovulation** (which presents as abnormal uterine bleeding), and **clinical** (hair-growth, deepening of the voice) or **biochemical** (elevated hormones) evidence of **hyperandrogenism**.

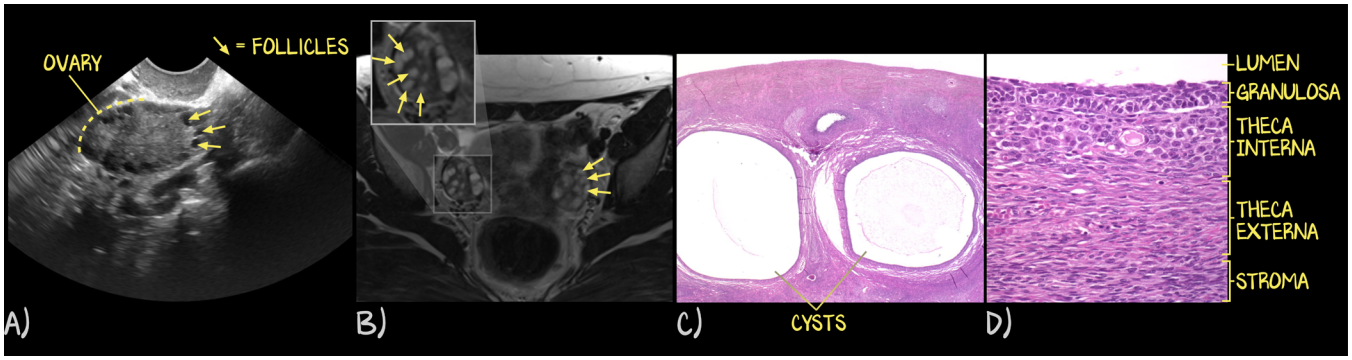

Figure 6.7: Polycystic Ovary Syndrome
(a) Longitudinal transvaginal ultrasound revealing a normal-sized ovary with numerous small fluid-filled cysts. These "cysts" are actually mature follicles. (b) Axial T2-weighted MRI (fluid is white) showing numerous follicles throughout the ovary. We've labeled the patient's right (left side of image), and the patient's left (right side of image) has been left unlabeled so that you have an unobstructed view. (c) Low-powered light microscopy demonstrating two extremely large follicles. Both are larger than a typical mature follicle because there was no LH surge and, therefore, no ovulation. Because there was no ovulation, there is no corpus luteum or its remnant, the corpus albicans. (c) Higher-magnification view of panel b showing the edge of a very mature follicle. The lumen is at the top of the image. There is a small layer of granulosa cells with their basement membrane, and then a well developed theca interna and theca externa. This reaffirms that what is seen as "cysts" on ultrasound are simply normal mature follicles, ready to ovulate should an LH surge occur.

Accept right now that there are many theories as to what causes this condition. The truth about PCOS is likely not what we are going to describe, and instead appears to be a genetic deficiency of receptor stimulation and increased resistance to a certain type of receptor.

What is certain is this: There is **insulin resistance** as well as **gonadotropin resistance**. Patients are typically overweight and hirsute and have insulin resistance or frank diabetes, fertility issues, and abnormal menses. An **ultrasound** of the ovaries will reveal many follicles. The diagnosis is treated with **metformin** (which improves diabetes/insulin resistance, but also gonadotropin resistance) and either **combined contraceptives** (any delivery form of both progestin and estrogen) if pregnancy is not desired or **clomiphene** with metformin (to induce ovulation and achieve pregnancy).

The following isn't certain, but it seems blindingly obvious to us. There are already **multiple anovulatory follicles**. They are a **symptom** and not a cause. If there is no ovulation, there is no progesterone and no silencing of the HPO axis. There is no ovulation because there is no LH surge because estrogen levels don't reach the critical threshold required by ?. Why not? Because peripheral tissues convert estrogen into androgens. Without ovulation to reset the system, estrogen levels reach a steady-state concentration below the ? threshold, with more estrogen being made by the mature follicles and removed by peripheral tissues, which convert the estrogen to androgens. Patients with PCOS are commonly obese, and obesity increases estrogen conversion to androgens, feeding forward the disease. A chronically elevated estrogen level without crossing threshold keeps follicles driving toward maximum maturation. A chronically elevated androgen level causes hirsutism.

Estrogen is inhibitory to FSH. There has been no ovulation to reset the axis. Estrogen builds a better pulsatility in the GnRH cells of the hypothalamus and better GnRH receptor expression on the gonadotropes of the anterior pituitary. Gene expression is altered so that less FSH is made relative to LH. This is reinforced by one of the laboratory criteria for the diagnosis—an elevated LH:FSH ratio. But what most people miss is that the **LH is usually normal** and the **FSH is normal**, but the LH:FSH ratio is > **3:1**. All that estrogen has already driven the hypothalamus to maximal pulsatility, has enabled the anterior pituitary to maximally hear the GnRH surge, has sustained every follicle in continued maturation, and has made every mature follicle express so many LH receptors that if the LH surge occurs, every mature follicle ovulates. The evidence behind this? If **clomiphene** (an estrogen receptor

partial agonist, which is supposed to act as an "inhibitor to estrogen") is given, many mature follicles ovulate. Why? They have been so primed for the LH surge for so long, that when it comes? Kerpow!

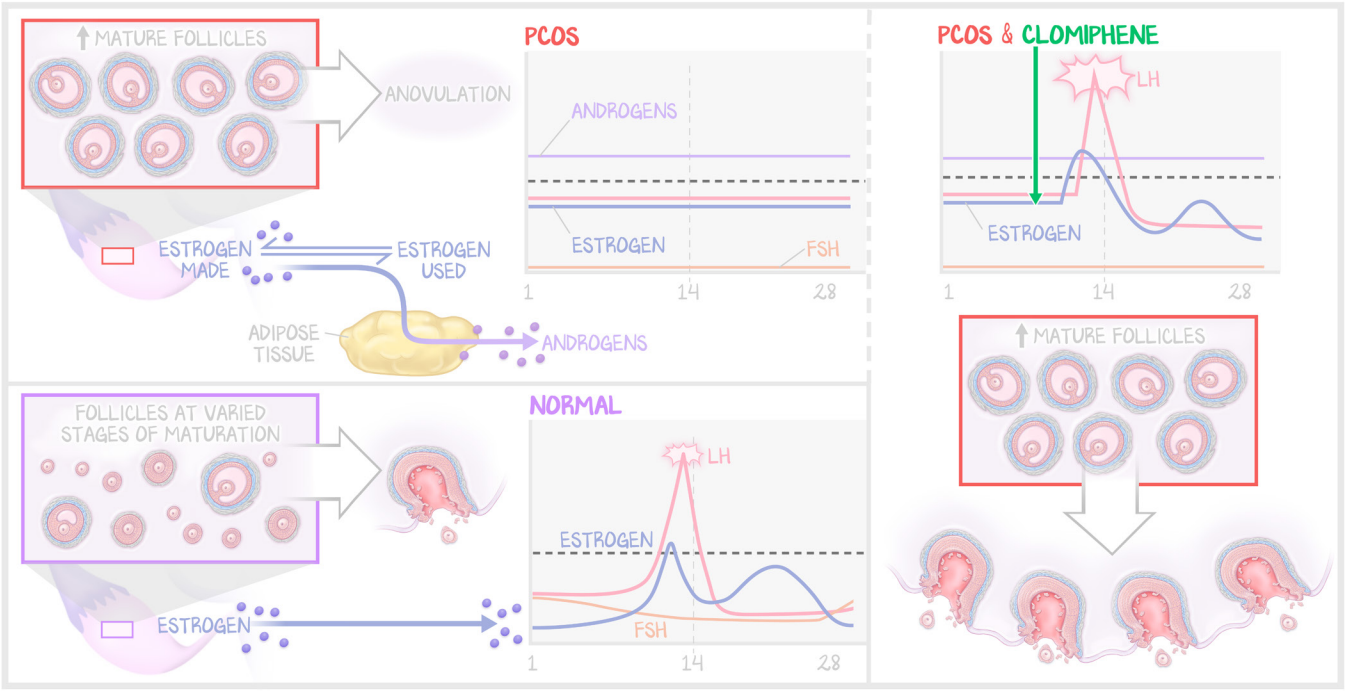

Figure 6.8: Dr. Williams' Theory
In a normal ovarian cycle, hormone levels change constantly. When estrogen crosses the threshold, there is an LH surge. In PCOS, the estrogen level is stagnant. It isn't elevated out of normal ranges, but it is statically near the threshold. This causes excess estrogen and anovulation. Because the axis is maximally ready for ovulation (due to the elevated estrogen level), there is a lot of LH around but not a lot of FSH—commonly a 3:1 ratio but within normal ranges. This arrangement stimulates the follicles to produce androgens. The androgens are converted into estrogen in the peripheral tissues, reaching an equilibrium between androgens made and androgens converted into estrogen. When clomiphene, a SERM that acts as a partial agonist in the hypothalamus, is added to that system, estrogen crosses the threshold, the LH surge happens, and many mature follicles (held that way by lots of LH expression from the gonadotropes) ovulate at once.

But why did a so-called estrogen blocker induce an LH surge if a critical threshold of estrogen is needed to incite ⍰? Because clomiphene is a **partial agonist**. In the alternative context of excess estrogen, clomiphene would act as a ceiling on the estrogen effect. Instead, when given to a woman with PCOS and an estrogen level just below the threshold concentration, the partial **agonist** pushes the estrogen receptor activation across the ⍰ threshold, resulting in an LH surge. Clomiphene works within five days, with five doses. At rest, the system is primed for the LH surge; it just got stuck at a level of estrogen slightly too low to activate the surge.

Now, how did that homeostasis get that way in the first place? No idea. But **metformin** and **progestin-containing contraception** help control symptoms and rein in the axis pharmacologically.

Menopause

Menopause is the **normal, appropriate** cessation of menses as a result of ovarian follicle depletion. It is clinically defined as **12 months of amenorrhea** in the absence of an underlying pathological etiology. The mean age of women at their final menstrual period is **51.5 years**. Before menopause, most women experience several years of irregular menses as ovarian follicle activity winds down—abnormal uterine bleeding, intermenstrual spotting, delayed or skipped menses, etc. This time is referred to as **menopausal transition**.

Symptoms of menopause are a result of **estrogen depletion** that accompanies follicular degeneration. The **most common** is the **vasomotor symptom** called hot flashes or hot flushes. Both terms are appropriate—some women experience intense heat, palpitations, perspiration, and anxiety, others experience the heat and vasodilation leading to a red flush, and some women experience both. Hot flashes can occur multiple times each day, and each episode lasts approximately 1–5 minutes. When they occur at night, they can cause significant sleep disturbances. They recur, on average, for nearly 5 years after the last menstrual period. Hot flashes occur in **60%–80% of women**. Treatment for hot flashes is twofold. First, **venlafaxine** and other SNRIs can mitigate both hot flashes and emotional changes (anxiety and depression) that can come with menopause. Back in the day, believing estrogen was cardioprotective and could prevent hot flashes, women were prescribed **hormone replacement therapy** with **just estrogen**. It didn't work—replacing estrogen does not reduce cardiovascular risk. But unopposed by progesterone, the excess estrogen did what excess estrogen does—increased the risk of endometrial hyperplasia and carcinoma, ovarian cancer, and breast cancer. Following a new understanding of progesterone's protective effects, dual hormone contraception (pills, IUDs, or other delivery methods) has come into use to taper women through menopause gradually. Although progesterone is protective against endometrial and ovarian cancer, it doesn't protect against breast cancer, and combined contraceptives increase the risk of deep vein thrombosis. Therefore, hormone replacement therapy cannot be prescribed universally to every woman. Each woman's risk and access to screening must be weighed against the severity of her symptoms.

Vulvovaginal changes and sexual dysfunction. Estrogen supports vaginal collagen and adipose tissue. As estrogen levels fall after menopause, the vaginal epithelium atrophies. It loses its rugae, leaving the vaginal walls smooth, pale, and friable. Declining estrogen also causes poor lubrication. These changes can contribute to dyspareunia and may lead to postcoital bleeding. Any woman who has postmenopausal vaginal bleeding needs an evaluation for endometrial cancer. Although bleeding due to the vaginal atrophy that accompanies aging is far more common than endometrial cancer, we want you to learn "get an ultrasound" so that you don't brush off bleeding and miss cancer.

We discussed **osteoporosis** in Endocrine: Parathyroid #4: *Unhealthy Bone*. Any perimenopausal or postmenopausal female should be on **calcium and vitamin D supplementation**. Every woman also needs a DEXA scan to evaluate bone density at age 65. Her rate of decline of bone density will be accelerated relative to her male genetic- and age-matched counterparts.